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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/623,075	BANERJEE ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment filed 19 April 2004 has been entered in full.

Election/Restrictions

2. Applicant's election with traverse of the invention of Group I, claims 1-11 and species (a) in the reply filed on 02 June 2006 is acknowledged. The traversal is on the grounds that the claims of Groups I and II are not independent and distinct, are drawn to a single inventive concept and a single inventive effort and the search and examination of both groups would not place a serious burden on the examiner. Applicants' remarks have been fully considered but are not found persuasive. MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required. While related, the inventions of Groups I and II are distinct in that the antibody of Group II can be used for affinity purification and/or detection assays in addition to the materially different therapeutic method of Group I, which differs in the method objectives, method steps, parameters, reagents used and different endpoints and are separately patentable (see MPEP 806.05(h)). Clearly, different searches and patentability issues are involved in the examination of each Group.

In regard to burden of search and examination, MPEP 803 states that a burden can be shown if the examiner shows either separate classification, different field of search or separate status in the art. In the instant case a burden has been established

in showing that the therapeutic method of Group I is classified in class 424, subclass 145.1, whereas the kit comprising the antibody of Group II is classified in class 530, subclass 388.23. The divergent classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and different patentability issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made FINAL.

3. Claims 12-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

4. Claims 1-11 are under examination to the extent that the anemia is anemia related to rheumatoid arthritis, i.e., the elected species.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 19 April 2004 has been fully considered by the examiner. A signed copy of the IDS submitted on 19 April 2004 is included with the instant Office Action.

Specification

6. The disclosure is objected to because of the following informalities:

a. The specification discloses various non-provisional US Application numbers that should be updated with their current status, i.e., "now abandoned" or "U.S. Patent

Number ....", or updated during the pendency of the present application should their status change. For example, see pg. 1, lines 13-29, pg. 6, lines 15 and 30 and pg. 7, line 27. Applicants' cooperation is requested in reviewing the entire disclosure for additional non-provisional U.S. Application Numbers that require updating.

b. The use of various trademarks have been noted in this application. For example, see pg. 6, lines 2-3, pg. 15, line 5, pg. 19, line 1 and pg. 39, lines 27-28. It should be capitalized wherever it appears and be accompanied by the generic terminology. Applicants' cooperation is requested in reviewing the entire disclosure for additional trademarks that require correction.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

c. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the treatment of anemia using human TNFα antibodies.

Appropriate correction is required.

Claim Objections

7. Claims 1-11 are objected to as being drawn to nonelected inventions.

Appropriate correction is required.

8. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. As depending from base claims 2, claim 4 recites that the antibody is D2E7, which does not incorporate the CDR3 amino acid substitutions of base claim 2 and thus, does not further limit the subject matter of previous claim 2. Applicant is reminded that a claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers and requires the dependent claim to further limit the subject matter claimed.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 4, and 8-11 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line, which produces an antibody having the exact chemical identity of antibody D2E7 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one

of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Fundamental Immunology, William E. Paul, M.D. ed., 3rd ed., pg. 242, 1993. Therefore, it would require undue experimentation to reproduce the claimed antibody species antibody D2E7.

The specification lacks complete deposit information for the deposit of anti-TNFα antibody D2E7. It is unclear whether antibodies possessing the identical properties of antibody D2E7 are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibody D2E7, a suitable deposit is required for patent purposes, evidence of public

availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of antibody D2E7 has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of antibody D2E7 is not made under the provisions of the Budapest Treaty, then in order to certify that the deposit complies with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

> (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:
> (b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:
> (c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the

furnishing of a sample of the deposited biological material, whichever is longest; and
(d) the deposits will be replaced if they should become nonviable or non-replicable.
Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed. See MPEP 2406 and 37 CFR 1.804(b).

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

11. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating pain or neuropathic pain in a subject comprising administering a human anti-human TNFα antibody or antigen-binding fragment thereof comprising a light chain comprising CDR1 of SEQ ID NO:7, CDR2 of SEQ ID NO:5 and CDR3 of SEQ ID NO:3 comprising the recited amino acid substitutions and a heavy chain comprising CDR1 of SEQ ID NO:8, CDR2 of SEQ ID

NO:6 and CDR3 of SEQ ID NO:4 comprising the recited amino acid substitutions, does not reasonably provide enablement for a method of treating pain or neuropathic pain in a subject comprising administering a human anti-human TNFα antibody or antigen-binding fragment thereof comprising a light chain comprising CDR3 of SEQ ID NO:3 comprising the recited amino acid substitutions and a heavy chain comprising a heavy chain comprising CDR3 of SEQ ID NO:4 comprising the recited amino acid substitutions as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered proteins and antibodies where the relative level of skill of those in the art is deemed to be high.

The claims are broadly drawn to a method of treating anemia related to rheumatoid arthritis in a subject comprising administering a human anti-human TNFα antibody or antigen-binding fragment thereof that dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light

chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12. Thus, the claims encompass anti-human TNFα antibodies that comprise mutant CDR3 regions of antibody D2E7 and do not comprise the heavy and light chain CDR1 and CDR2 regions from antibody D2E7 for the clinical treatment of anemia related to rheumatoid arthritis.

The specification discloses only human anti-human TNFα antibodies and antigen-binding fragments thereof that comprise all six CDRs, three from the heavy chain and three from the light chain of human anti-human TNFα antibody D2E7 (see examples). The specification does not teach human anti-human TNFα antibodies or antigen-binding fragments thereof that only comprise the mutant CDR3 regions of the heavy and light chains of antibody D2E7, which do not contain the CDR1 and CDR2 regions of antibody D2E7 and do not bind human TNFα. There are no working examples of human anti-human TNFα antibodies or antigen-binding fragments thereof that only comprise the mutant CDR3 regions of the heavy and light chains of antibody D2E7, wherein the antibodies or antigen-binding fragments thereof bind human TNFα and dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less. The scope of the

claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, March 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that human anti-human TNFα antibodies and antigen-binding

fragments thereof, which do not contain all of the heavy and light chain CDRs of antibody D2E7 in their proper order and in the context of framework sequences which maintain their correct spatial orientation have the requisite human TNFα -binding function. There is insufficient guidance and direction to assist those skilled in the art in producing human anti-human TNFα antibodies that only comprise mutant CDR3 regions of antibody D2E7 that bind human TNFα. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing human anti-human TNFα antibodies, which contain less than the full complement of CDRs of antibody D2E7 and comprising the recited heavy and light chain CDR3 amino acid substitutions, wherein the antibody binds human TNFα and dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less and effectively treats anemia related to rheumatoid arthritis in a subject. One of skill in the art would neither expect nor predict the appropriate functioning of the human anti-human TNFα antibodies as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E. and Rudikoff et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed therapeutic method comprising human anti-human TNFα antibodies, which contain less than the full complement of CDRs of antibody D2E7 with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed human anti-human TNFα antibodies and absent working examples providing evidence which is

reasonably predictive that the claimed human anti-human TNFα antibodies bind human TNFα and dissociates from human TNFα with a K_{off} of 1 x 10^{-3} s^{-1} or less, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Salfeld et al [a] (WO 97/29131, publication date 8/14/1997).

The claims are drawn to a method of treating anemia related to rheumatoid arthritis in a subject a therapeutically effective amount of a neutralizing, high affinity TNFα antibody or antigen-binding fragment thereof such that the pain or neuropathic pain is treated, wherein the antibody is an isolated human antibody or antigen-binding fragment thereof that dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less, and wherein the isolated human antibody or antigen-binding fragment

thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the isolated human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and the antibody is D2E7, or is antibody D2E7 and one additional therapeutic agent.

Salfeld et al [a] teach a method of treating rheumatoid arthritis comprising administering a therapeutically effective amount of a human anti-human TNFα antibody or antigen-binding fragment thereof identical to the claimed human anti-human TNFα antibodies, i.e., dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and has a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less, and the human antibody or antigen-binding fragment thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3

by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and the antibody is D2E7 and is administered with one or more additional therapeutic agents (see entire document, particularly pp. 3-4, 5-6, 12-15, 29-31 and 35-40). Thus, the administration of the human anti-human TNFα antibodies for the treatment of rheumatoid arthritis would necessarily treat anemia related to rheumatoid arthritis, which is a common complication of rheumatoid arthritis as evidenced by http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.htm (see middle of pg. 3).

Thus, Salfeld et al [a] anticipate the claims.

14. Claims 1-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Salfeld et al [b] (US Patent 6,509,015 B1, 2/9/1996, IDS reference A3 filed 4/19/2004).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims have been described supra.

Salfeld et al [b] teach a method of treating rheumatoid arthritis comprising administering a therapeutically effective amount of a human anti-human TNFα antibody or antigen-binding fragment thereof identical to the claimed human anti-human TNFα antibodies, i.e., dissociates from human TNFα with a K_d of 1×10^{-8} M or less and has a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less, and the human antibody or antigen-binding fragment thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and the antibody is D2E7 (see entire document, particularly columns 3-4, 9-13, 22 and 25). Thus, the administration of the

human anti-human TNFα antibodies for the treatment of rheumatoid arthritis would necessarily treat anemia related to rheumatoid arthritis, which is a common complication of rheumatoid arthritis as evidenced by http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.htm (see middle of pg. 3).

Thus, Salfeld et al [b] anticipate the claims.

15. Claims 1 and 3-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Kempeni J (Ann. Rheum. Dis., 58(Suppl I):I70-I72, 1999) as evidenced by the specification.

The claims have been described supra.

Kempeni teaches a method of treating rheumatoid arthritis patients comprising administering human anti-TNFα monoclonal antibody D2E7, which is identical the presently claimed antibody. As evidenced by the specification, human anti-TNFα monoclonal antibody D2E7 necessarily comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2 and comprises the recited binding kinetics and neutralization properties as evidenced by the specification (e.g., see pg. 15). Further, Kempeni et al teach that the administration of human anti-TNFα monoclonal antibody D2E7 in combination with methotrexate in rheumatoid arthritis patients. Thus, the administration of anti-TNFα monoclonal antibody D2E7 or D2E7 in combination with methotrexate for the treatment of rheumatoid arthritis would necessarily treat anemia related to rheumatoid arthritis, which

is a common complication of rheumatoid arthritis as evidenced by

http://www.emedicinehealth.com/rheumatoid_arthritis/article_em.htm (see middle of pg. 3).

Thus, Kempeni anticipates the claims as evidenced by the specification.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17 and 49 of U.S. Patent No. 6,509,015 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a method of treating anemia related to rheumatoid arthritis in a subject comprising administering an effective amount

of neutralizing, high affinity human anti-human TNFα antibodies and antigen-binding fragments thereof having the presently claimed binding kinetics, neutralization properties and structures/sequences and claims 17 and 49 of U.S. Patent No. 6,509,015 B1 are drawn to a method of inhibiting human TNFα activity in a human subject suffering from rheumatoid arthritis and treating a human subject suffering from rheumatoid arthritis in which TNFα activity is detrimental comprising administering to the human subject a human anti-human TNFα antibody or antigen-binding fragment thereof that is identical to the neutralizing, high affinity human anti-human TNFα antibodies and antigen-binding fragments thereof of the present claims, i.e., identical structures/sequences, binding kinetics and neutralization properties. Thus, the administration of the human anti-human TNFα antibodies and antigen-binding fragments thereof for the treatment of rheumatoid arthritis would necessarily treat anemia, which is a common complication of rheumatoid arthritis.

Claims 1-11 are directed to an invention not patentably distinct from claim 17 and 49 of commonly assigned U.S. Patent No. 6,509,015 B1. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,509,015 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can,

under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

18. Claims 1-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-8 and 10-15 of copending Application No. 11/435,844. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a method of treating anemia related to rheumatoid arthritis in a subject comprising administering an effective amount of neutralizing, high affinity human anti-human TNFα antibodies and antigen-binding fragments thereof having the recited binding kinetics, neutralization properties and sequences and claims 1, 4-8 and 10-15 of copending Application No. 11/435,844 are drawn to a method for treating a human subject suffering from erosive polyarthritis comprising administering to the subject a TNFα antibody or antigen-binding fragment thereof such that erosive polyarthritis is treated, wherein the antibody or antigen-binding fragment thereof is human, dissociates from human TNFα with a K_d of 1×10^{-8} M or less and has a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in

a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less, and the human antibody or antigen-binding fragment thereof antibody has the following characteristics: (a) dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance; (b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; (c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, and wherein the human antibody or antigen-binding fragment thereof comprises a light chain variable region comprising SEQ ID NO:1 and a heavy chain variable region comprising SEQ ID NO:2, all properties of the human anti-human TNFα antibodies and antigen-binding fragments thereof of the present claims. Further, the subject has a disorder in which TNFα activity is detrimental and is selected from psoriatic arthritis, ankylosing sopondylitis and juvenile rheumatoid arthritis. Therefore, the therapeutic method recited in claims 1, 4-8 and 10-15 of copending Application No. 11/435,844, comprising administering human anti-human TNFα antibodies and antigen-binding fragments thereof identical to the presently claimed anti-TNFα antibodies reads upon claims 1-11 of the instant application.

Claims 1-11 are directed to an invention not patentably distinct from claim 1, 4-8 and 10-15 of commonly assigned copending Application No. 11/435,844. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 11/435,844, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 1-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23, 58, 60-70

and 73-84 of copending Application No. 10/163,657 in view of Salfeld et al [a] (WO 97/29131, publication date 8/14/1997). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 1-23, 58, 60-70 and 73-84 of copending Application No. 10/163,657 are drawn to methods for treating a disorder, including autoimmune disease and rheumatoid arthritis, comprising administering an anti-TNFα antibody or antigen-binding fragment thereof on a biweekly dosing regimen, wherein the antibody or antigen-binding fragment thereof is a human antibody identical to the human anti-human TNFα antibodies claimed in the instant application, i.e., having identical structures/sequences, binding kinetics and neutralization properties. Claims 1-23, 58, 60-70 and 73-84 of copending Application No. 10/163,657 do not teach the administration of at least one additional therapeutic agent. This deficiency is made up for in the teachings of Salfeld et al [a].

Salfeld et al [a] have been described supra.

The claims in the instant application are obvious variants of claims 1-23, 58, 60-70 and 73-84 of copending Application No. 10/163,657 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method of claims 1-23, 58, 60-70 and 73-84 of copending Application No. 10/163,657 comprising administering the human anti-human TNFα antibodies for the treatment of rheumatoid arthritis and optionally administer the human

anti-human TNFα antibodies in combination with at least one additional therapeutic agent in view of the teachings of Salfeld et al [a].

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to apply the method of claims 1-23, 58, 60-70 and 73-84 of copending Application No. 10/163,657 comprising administering the human anti-human TNFα antibodies for the treatment of rheumatoid arthritis and optionally administer the human anti-human TNFα antibodies in combination with at least one additional therapeutic agent in view of the teachings of Salfeld et al [a] because Salfeld et al [a] teach the administration of the human anti-human TNFα antibodies of claims 1-23, 58, 60-70 and 73-84 of copending Application No. 10/163,657, optionally in combination with at least one additional therapeutic agent for the treatment of rheumatoid arthritis in a subject. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating rheumatoid arthritis in a subject comprising administering the human anti-human TNFα antibodies of claims 1-23, 58, 60-70 and 73-84 of copending Application No. 10/163,657 and optionally administer the human anti-human TNFα antibodies in combination with at least one additional therapeutic agent as taught by Salfeld et al [a]. The therapeutic administration of the human anti-human TNFα antibodies and antigen-binding fragments thereof for the treatment of rheumatoid arthritis in a subject would necessarily treat anemia, which is a common complication of rheumatoid arthritis.

Claims 1-11 are directed to an invention not patentably distinct from claims 1-23, 58, 60-70 and 73-84 of commonly assigned copending Application No. 10/163,657. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 10/163,657, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-19 of

copending Application No. 11/233,252 in view of Salfeld et al [a] (WO 97/29131, publication date 8/14/1997). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 15-19 of copending Application No. 11/233,252 are drawn to a method for treating a subject suffering from various disorders in which TNFα activity is detrimental including an rheumatoid arthritis comprising administering a pharmaceutical composition comprising an isolated human anti-human TNFα antibody or antigen-binding fragment thereof that dissociates from human TNFα with a K_d of 1×10^{-8} M or less and has a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less. Claims 15-19 of copending Application No. 11/233,252 do not specifically teach human anti-human TNFα antibodies or antigen-binding fragments thereof having a K_{off} of 1×10^{-3} s^{-1} or less and the light and heavy chain CDR3 sequences (SEQ ID Nos:3-4) or variants thereof or comprising the light chain variable region of SEQ ID NO:1 and the heavy chain variable region of SEQ ID NO:2 or wherein the anti-human TNFα antibody is antibody D2E7 and in combination with at least one additional therapeutic agent. These deficiencies are made up for in the teachings of Salfeld et al [a].

Salfeld et al [a] have been described supra.

The claims in the instant application are obvious variants of claims 15-19 of copending Application No. 11/233,252 because it would have been *prima facie* obvious

to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating rheumatoid arthritis in a subject comprising administering the human anti-human TNFα antibodies of Salfeld et al [a], and in combination with at least one additional therapeutic agent in view of the teachings of Salfeld et al [a].

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a method for treating rheumatoid arthritis in a subject comprising administering the human anti-human TNFα antibodies of Salfeld et al [a], and in combination with at least one additional therapeutic agent in view of claims 15-19 of copending Application No. 11/233,252 and Salfeld et al [a] because Salfeld et al teach the administration of the human anti-human TNFα antibodies of claims 15-19 of copending Application No. 11/233,252, and in combination with at least one additional therapeutic agent for the treatment of rheumatoid arthritis in a subject. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating rheumatoid arthritis in a subject comprising administering the human anti-human TNFα antibodies of Salfeld et al [a], and in combination with at least one additional therapeutic agent in view of the teachings of Salfeld et al [a]. The therapeutic administration of the human anti-human TNFα antibodies and antigen-binding fragments thereof for the treatment of rheumatoid arthritis in a subject would necessarily treat anemia, which is a common complication of rheumatoid arthritis.

Claims 1-11 are directed to an invention not patentably distinct from claims 15-19 of commonly assigned copending Application No. 11/233,252. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 11/233,252, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 1-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 10/622,205; claims 1-27 of copending Application No. 10/622,210; claims 1-26 of copending Application No. 10/622,683; claims 1-24 of copending Application No. 10/622,928; claims 1-14 of copending Application No.

10/622,932; claims 1-23 of copending Application No. 10/623,039; claims 1-24 of copending Application No. 10/623,065; claims 1-16 of copending Application No. 10/623,035; claims 1-34 of copending Application No. 10/623,076; claims 1-16 of copending Application No. 10/623,318 in view of Salfeld et al [a] (WO 97/29131, publication date 8/14/1997). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

The above cited copending applications claims are drawn to the administration of human anti-human TNFα antibodies and antigen-binding fragment thereof that are identical to the neutralizing, high affinity human anti-human TNFα antibodies and antigen-binding fragments thereof of the present claims, i.e., identical structures/sequences,.binding kinetics and neutralization properties, for the treatment of various disorders. The above claims of the copending applications do not specifically teach the treatment of rheumatoid arthritis and wherein antibody D2E7 is administered with at least one additional therapeutic agent. These deficiencies are made up for in the teachings of Salfeld et al [a].

Salfeld et al [a] have been described supra.

The claims in the instant application are obvious variants of the above copending applications claims because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating rheumatoid arthritis in a subject comprising administering the human anti-human TNFα antibodies recited the above copending applications, identical to the

presently claimed anti-TNFα antibodies and in combination with at least one additional therapeutic agent in view of the teachings of Salfeld et al [a].

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a method for treating rheumatoid arthritis in a subject comprising administering the human anti-human TNFα antibodies recited the above copending applications, identical to the presently claimed anti-TNFα antibodies and in combination with at least one additional therapeutic agent in view of the teachings of Salfeld et al [a] because Salfeld et al [a] teach the administration of the human anti-human TNFα antibodies claimed in each of the copending applications and in combination with at least one additional therapeutic agent for the treatment of rheumatoid arthritis in a subject. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for treating rheumatoid arthritis in a subject comprising administering the human anti-human TNFα antibodies recited in the above copending applications and in combination with at least one additional therapeutic agent in view of the teachings of Salfeld et al [a]. The therapeutic administration of the human anti-human TNFα antibodies and antigen-binding fragments thereof (structurally identical to the presently claimed anti-TNFα antibodies) for the treatment of rheumatoid arthritis in a subject would necessarily treat anemia, which is a common complication of rheumatoid arthritis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827